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1,2,3-Triazoles containing Thiazole-Piperazine Moieties: Synthesis, Biological Assessment and Molecular Docking

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A novel series of thiazole-triazole-piperazine multi hybrids was designed for antimicrobial activity and the synthetic method for this series has been developed by copper catalyzed 1,3-dipolar cycloaddition of thiazole-based azide with Boc-piperidine based alkyne in the presence of $CuSO_4$ and sodium ascorbate. Boc deprotection followed by alkylation of piperidine moiety in hybrid derivatives was also carried out. All the target compounds were confirmed using FTIR, ^{1}H NMR, ^{13}C NMR and LC-MS spectral techniques. These compounds were screened for the antimicrobial activity against bacteria and fungi. The antimicrobial activities are also comparable to standard drugs ampicillin and clotrimazole. All the molecules showed good to moderate activity and supported by molecular docking studies and ADME prediction.

Keywords: Thiazole, 1,2,3-Triazole, Piperazine, Antimicrobial, Molecular docking.

INTRODUCTION

1,3-Thiazole is an attractive motif found in a vast array of bioactive heterocycles which are of synthetic origin, exhibit diverse pharmacological activities such as anticancer, anti-inflammatory, antioxidant, anti-psychotropic, anti-allergic, antimicrobial, anti-HIV and antibacterial activities [1-3]. Several thiazole containing drugs have been approved for clinical use, such as dasatinib, sulphathiazole, ravuconazole, ritonavir, dabrafenib and meloxicam [4-7].

On the other hand, 1,2,3-triazole ring drawing the attention of researchers due to its derivatives are known to exhibit various pharmacological properties such as antimicrobial [8,9], anti-tuberculosis [10], anticancer [11,12], anticonvulsant [13], anti-inflammatory [14] and antiviral [15]. Triazoles are also used in agriculture field, used in the control of variety of fungal diseases in fruits, vegetables, legumes and grain crops, both as pre and postharvest applications [16]. The preference of 1,2,3-triazoles as a linker among two other heterocyclic functions in hybrids has recently attracted the attention of scientists as several useful therapeutic uses are found [17,18]. Another important class of heterocyclic pharmacophores constitutes the piperazines and substituted piperazines, most of the piperazines are well known as antimicrobial agents [19]. Also, many piperazine molecules are representatives for antibacterial [20], antifungal [21], antimalarial [22], antidepressant [23], anti-tumor [24], alpha-adrenoceptor antagonist [25] and 5-HT7 receptor antagonist activities [26]. Buspirone (antianxiety) and trazodone (antidepressant) are recently approved drug molecules [27,28]. Nearly a dozen of FDA approved piperazine based compounds are marketed anticancer drugs [29]. The cytotoxic activity of piperazine compounds of natural origin is also well known [30].

In recent decade, the design and synthesis of potential biological agents to treat various diseases, takes place through the molecular hybridization of two or more heterocyclic pharmacophores, which play a significant role in organic as well as medicinal chemistry. Imidazothiazole-piperazine (I) and triazole-piperazine (II) for anti-TB activity [31,32] thiazole-triazoles hybrids (III, IV) for anti-anxiety and anti-inflammatory activities [33,34] are well reported. Triazole-pyrzolo fused thiazole-triazole hybrids (V) [35] and triazole linked thiazole-1,2-isoxazole (VI) as multi-hybrid molecules are noted for anticancer activity [36] (Fig. 1).

All these observations and in continuation of our present research efforts on building the novel hybrid molecules with more than four nitrogen atoms expecting the potent antimicrobial activity, thiazole-triazole-piperazine as a multi-hybrid heterocycle is designed and its synthesis is taken up in a multi-step synthetic path. The hybrid compounds are screened for antimicrobial activity against bacteria and fungi.

EXPERIMENTAL

The melting point has determined in open capillaries and are uncorrected. The Bruker AV instrument is used to record ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra. $CDCl_3$, DMSO-d_6 solvents were used to record NMR spectra of samples. The ESI-MS spectra were recorded Agilent 1100 LC-Q TOF instrument. TLC plates coated with Merck silica gel 60 F_{254} were used to monitor the reactions.

Synthesis of *N*-(4-(3-bromophenyl)thiazol-2-yl)-2-chloroacetamide (2): To a stirred solution of compound **1** (2 g, 7.843 mmol, 1.0 eq.) in DCM (20 mL) was added DIPEA (1.77 mL, 10.196 mmol, 1.3 equiv.) followed by chloroacetyl chloride (0.68 mL, 8.627 mmol, 1.1 equiv.) at 0 ºC. Then the reaction mixture was allowed to stir at 25 ºC for 2 h. Cold water was added to the content of the reaction and extracted with DCM. The organic layer was dried and concentrated under reduced pressure to get the crude (3 g), which further gave product **2** on

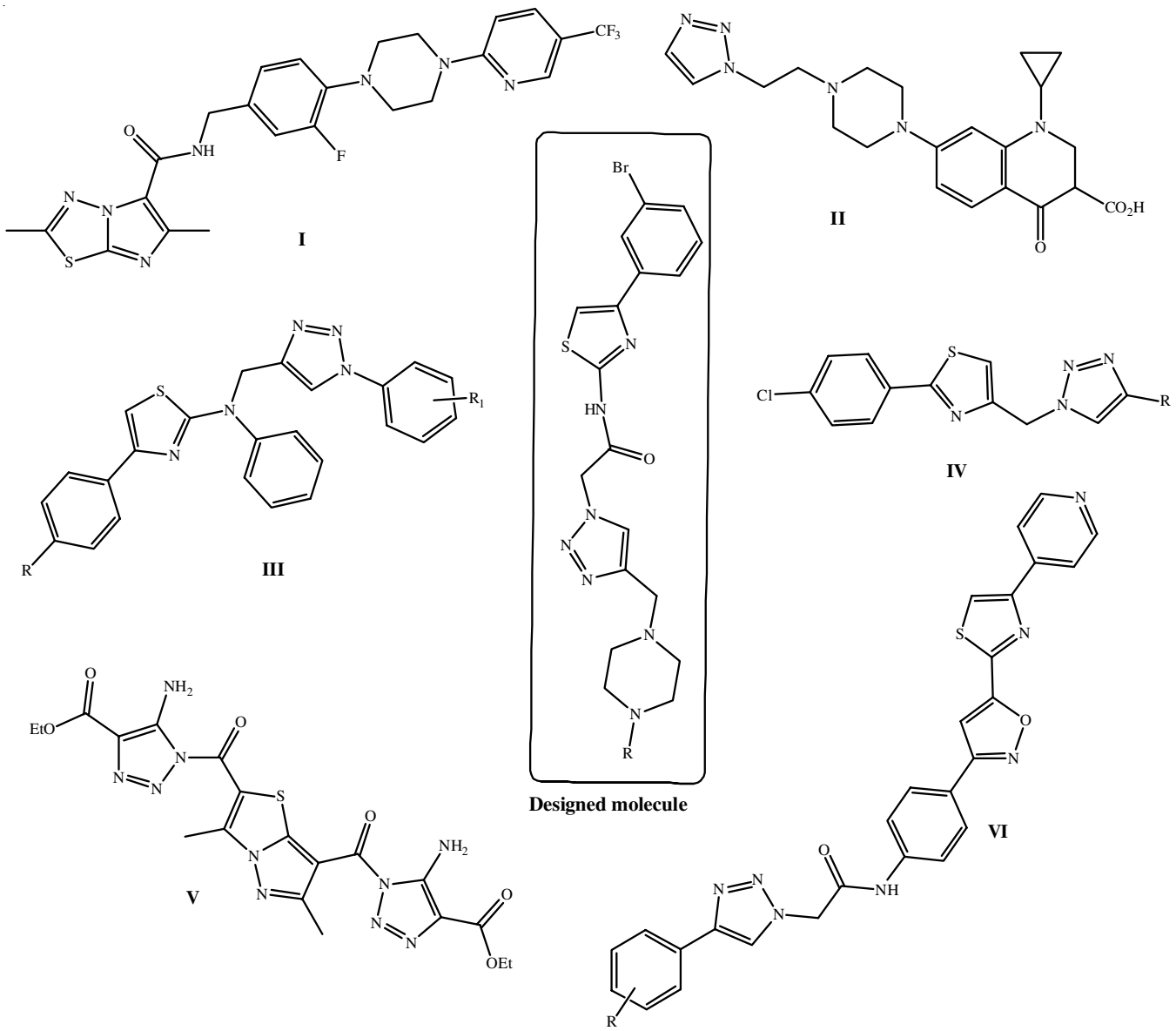


Fig. 1. Thiazole based hybrid compounds with diverse biological activity

purification by silica gel (60-120 mesh) column chromatography using gradient elution with 30% EtOAc/hexane (yield: 2.2 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.01 (t, *J* = 1.6 Hz, 1H), 7.76-7.73 (m, 1H), 7.47-7.44 (m, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.22 (s, 1H), 4.30 (s, 2H), purity: 99% by LC-MS, ESI *m/z*: 329.9 $[M+H]^+$.

Synthesis of 2-azido-*N*-(4-(3-bromophenyl)thiazol-2-yl)acetamide (3): Compound **2** (2.2 g, 6.66 mmol, 1.0 eq.) was taken in anhydrous DMF (15 mL), added NaN_3 (4.26 g, 66.67 mmol, 10.0 equiv.) at 25 ºC and stirred at 60 ºC. After 2 h, reaction mixture was poured into ice water (10 mL) and extracted with EtOAc (2 × 25 mL). The crude product was obtained by drying and concentrating the organic layer under reduced pressure, which was purified by silica gel (60-120 mesh) column chromatography using gradient elution with 30% EtOAc/hexane to get compound **3** (1.6 g, yield: 72%) as pale-yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.67 (s, 1H), 8.01 (t, *J* = 1.6 Hz, 1H), 7.76-7.73 (m, 1H), 7.47-7.44 (m, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 4.28 (s, 2H). Purity: 98% by LC-MS, ESI *m/z*: 338.0 $[M+H]^+$.

Synthesis of *tert.*-butyl 4-((1-(2-((4-(3-bromophenyl)-thiazol-2-yl)amino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)-methyl)piperazine-1-carboxylate (5): A mixture of compound **3** (800 mg, 2.377 mmol, 1.0 equiv.) and compound **4** (530 mg, 2.377 mmol, 1.0 equiv.)was taken in *tert.*-butanol/H_2O (1:1) (30 mL) and sodium ascorbate (141 mg, 0.713 mmol, 0.3 equiv.) followed by $CuSO_4{\cdot}5H_2O$ (59 mg, 0.237 mmol, 0.1 equiv.) at 25 ºC were added. The reaction mixture was stirred at 25 ºC for 18 h. Then the reaction mixture was poured into water (100 mL), the separated solid was filtered, washed with distilled water (20 mL), dried under vacuum to get compound **5** (1 g, yield: 77%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.81 (s, 1H), 8.01 (s, 1H), 8.07 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.83 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 5.28 (s, 2H), 3.64 (s, 2H), 3.31 (s, 4H), 2.48-2.32(m, 4H), 1.39 (s, 9H). LC-MS *m/z*: 559.8 $[M-H]^+$.

Synthesis of *N*-(4-(3-bromophenyl)thiazol-2-yl)-2-(4-(piperazin-1-ylmethyl)-1*H*-1,2,3-triazol-1-yl)acetamide hydrochloride (6): To a stirred solution of compound **5** (850 mg, 1.517 mmol, 1.0 equiv.) in DCM (10 mL) was added to 4 N HCl in dioxane (0.75 mL, 3.0357 mmol, 2.0 equiv.) at 0 ºC and then stirred at 25 ºC for 18 h. The reaction mixture was concentrated to obtain compound **6** as crude residue (680 mg, 93%), which was used for next step without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 12.93 (s,1H), 9.72 (brs, 2H), 8.45 (s, 1H), 8.11 (t, *J* = 1.6 Hz, 1H), 7.92 (dt, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.55-7.52 (m, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 5.61 (s, 2H), 4.58 (s, 2H), 3.46 (brs, 8H). LC-MS *m/z*: 464.1 $[M + 2H]^+$.

Synthesis of 2-(4-((4-substitued piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-(3-bromophenyl)thiazol-2-yl)-acetamide (8a-l): To a compound **6** (0.2 mmol, 1.0 equiv.) in acetonitrile (5 mL) was added Et_3N (0.602 mmol, 3.0 equiv.) followed by compound **7a-l** (0.2 mmol, 1.0 equiv.) at 25 ºC and stirred for 18 h. After the completion of reaction, the reaction mixture was concentrated to obtain the crude residue, which was purified by silica gel column chromatography using eluent 5-10% MeOH/DCM to get the corresponding product **8a-l**.

2-(4-((4-Benzylpiperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-(3-bromophenyl) thiazol-2-yl)acetamide (8a): Off-white solid, yield: 78%, m.p.: 196-199 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.75 (s, 1H), 8.11 (t, *J* = 1.6 Hz, 1H), 8.02 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.53 (dq, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.34-7.21 (m, 5H), 5.46 (s, 2H), 3.58 (s, 2H), 3.47 (s, 2H), 2.48-2.30 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.09, 157.51, 147.23, 143.20, 136.30, 130.98, 130.49, 128.81, 128.26, 128.11, 126.89, 125.47, 124.54, 122.18, 110.00, 61.94, 52.42, 52.36, 52.12, 51.31. Purity: 98% by LC-MS, ESI *m/z*: 551.9 $[M+H]^+$.

2-(4-((4-(3-Bromobenzyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-(3-bromophenyl)thiazol-2-yl)-acetamide (8b): Pale-yellow solid, yield: 75%, m.p.: 215-217 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.83 (s, 1H), 8.11 (t, *J* = 1.6 Hz, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.53 (dq, *J* = 8.0 Hz, 1H), 7.48 (s, 1H), 7.46-7.39 (m, 2H), 7.32-7.26 (m, 2H), 5.47 (s, 2H), 3.60 (s, 2H), 3.46 (s, 2H), 2.49-2.30 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.09, 157.50, 147.23, 136.30, 131.26, 130.97, 130.49, 130.32, 129.76, 128.26, 127.78, 125.52, 124.55, 122.18, 121.54, 110.00, 61.01, 52.31, 52.09, 51.32. Purity: 99% by LC-MS, ESI *m/z*: 631.9 $[M+H]^+$.

2-(4-((4-(4-Bromobenzyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(4-(3-bromophenyl)thiazol-2-yl)-acetamide (8c): Pale-yellow solid, yield: 72%, m.p.: 189-193 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.84 (s, 1H), 8.11 (t, *J* = 1.6 Hz, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.53 (dq, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 5.47 (s, 2H), 3.60 (s, 2H), 3.43 (s, 2H), 2.49-2.28 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.10, 157.49, 147.23, 136.30, 131.01, 130.97, 130.49, 128.26, 125.53, 124.55, 122.17, 119.91, 110.00, 60.97, 52.28, 52.05, 51.32. Purity: 98% by LC-MS, ESI *m/z*: 631.9 $[M+H]^+$.

***N*-(4-(3-Bromophenyl)thiazol-2-yl)-2-(4-((4-(3-chlorobenzyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (8d):** Off-white solid, yield: 69%, m.p.: 206-209 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.87 (s, 1H), 8.11 (t, *J* = 1.6 Hz, 1H), 8.04 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.53 (dq, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.38-7.24 (m, 4H), 5.49 (s, 2H), 3.61 (s, 2H), 3.47 (s, 2H), 2.49-2.30 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 157.48, 147.22, 136.31, 132.88, 130.96, 130.48, 130.01, 128.35, 128.26, 127.41, 126.89, 125.58, 124.55, 122.17, 110.00, 60.99, 52.25, 52.02, 51.34. Purity: 92% by LC-MS, ESI *m/z*: 587.9 $[M+H]^+$.

***N*-(4-(3-Bromophenyl)thiazol-2-yl)-2-(4-((4-(4-fluorobenzyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (8e):** Off-white solid, yield: 71%, m.p.: 187-190 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.81 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.83 (s, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 5.47 (s, 2H), 3.59 (s, 2H), 3.43 (s, 2H), 2.46-2.26 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 164.95, 162.41, 160.00, 157.51, 147.21, 136.31, 134.21, 130.96, 130.64, 130.57, 130.48, 128.27, 124.55, 122.17, 114.92, 114.71,

110.00, 61.10, 52.38, 52.24, 52.15, 51.40. Purity: 95% by LC-MS, ESI *m/z*: 571.9 $[M+H]^+$.

***N*-(4-(3-Bromophenyl)thiazol-2-yl)-2-(4-((4-(4-methoxybenzyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)-acetamide (8f):** Off-white solid, yield: 73%, m.p.: 153-156 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.81 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.47 (s, 2H), 3.73 (s, 3H), 3.61 (s, 2H), 3.42 (s, 2H), 2.48-2.28 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.08, 158.34, 157.50, 147.23, 136.29, 130.98, 130.50, 130.21, 128.26, 125.52, 124.55, 122.18, 113.52, 110.00, 61.15, 54.96, 52.25, 52.14, 51.89, 51.31. Purity: 95% by LC-MS, ESI *m/z*: 582.0 $[M+H]^+$.

***N*-(4-(3-Bromophenyl)thiazol-2-yl)-2-(4-((4-(4-nitrobenzyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (8g):** Yellow solid, yield: 70%, m.p.: 192-194 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.83 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 8.11 (t, *J* = 1.6 Hz, 1H), 8.04 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.53 (dq, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 3.60 (s, 4H), 2.49-2.30 (m, 8H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.07, 157.48, 147.24, 146.56, 136.29, 130.97, 130.50, 129.70, 125.72, 124.55, 123.32, 122.18, 110.01, 60.81, 52.22, 52.08, 51.95, 51.33. Purity: 93% by LC-MS, ESI *m/z*: 599.0 $[M+H]^+$.

***N*-(4-(3-Bromophenyl)thiazol-2-yl)-2-(4-((4-pentylpiperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)acetamide (8h):** Off-white solid, yield: 74%, m.p.: 214-217 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.74 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 5.46 (s, 2H), 3.57 (s, 2H), 2.48-2.29 (m, 8H), 2.24 (t, *J* = 7.2 Hz, 2H), 1.45-1.34 (m, 2H), 1.32-1.18 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 165.12, 157.60, 147.22, 136.32, 130.97, 130.48, 128.26, 125.44, 124.54, 122.18, 109.98, 57.78, 52.67, 52.42, 52.18, 51.33, 29.12, 25.87, 22.00, 13.91. Purity: 98% by LC-MS, ESI *m/z*: 532.0 $[M+H]^+$.

Ethyl 4-(4-((1-(2-((4-(3-bromophenyl)thiazol-2-yl)-amino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)butanoate (8i): Off-white solid, yield: 67%, m.p.: 183-186 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.79 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.83 (s, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 5.46 (s, 2H), 4.03 (q, *J* = 14, 7.2 Hz, 2H), 3.56 (s, 2H), 2.47-2.30 (m, 8H), 2,30-2.20 (m, 4H), 1,70-1.60 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 172.82, 165.10, 157.55, 147.22, 143.26, 136.31, 130.98, 130.49, 128.26, 125.44, 124.54, 122.18, 109.99, 59.62, 56.87, 52.57, 52.32, 52.19, 51.31, 31.48, 21.64, 14.08. Purity: 98% by LC-MS, ESI *m/z*: 577.9 $[M+H]^+$.

Ethyl 6-(4-((1-(2-((4-(3-Bromophenyl)thiazol-2-yl)-amino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)hexanoate (8j): Off-white solid, yield: 70%, m.p.: 148-151 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.77 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 4.04 (q, *J* = 14.0, 7.2 Hz, 2H), 3.59 (s, 2H), 2.48-2.29 (m, 8H), 2.27 (t, *J* = 7.6 Hz, 4H), 1,57-1.47 (m, 2H), 1.46-1.37 (m, 2H), 1.31-1.21 (m, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.88, 165.08, 157.53, 147.22, 143.13, 136.27, 130.99, 130.51, 128.25, 125.52, 124.54, 122.17, 109.98, 59.63, 57.33, 52.41, 52.23, 51.76, 51.31, 33.41, 26.21, 25.50, 24.30, 14.09. Purity: 98% by LC-MS, ESI *m/z*: 606.0 $[M+H]^+$.

Ethyl 8-(4-((1-(2-((4-(3-bromophenyl)thiazol-2-yl)-amino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)octanoate (8k): Off-white solid, yield: 68%, m.p.: 141-143 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.77 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 4.04 (q, *J* = 14.4, 7.2 Hz, 2H), 3.59 (s, 2H), 2.48-2.29 (m, 8H), 2.26 (t, *J* = 7.6 Hz, 4H), 1,57-1.47 (m, 2H), 1.46-1.36 (m, 2H), 1.31-1.21 (m, 6H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 172.86, 165.09, 157.52, 147.23, 136.30, 130.98, 130.50, 128.26, 125.49, 124.54, 122.18, 110.00, 59.59, 52.47, 52.27, 51.82, 51.31, 33.44, 28.46, 28.31, 26.58, 24.35, 14.10. Purity: 98% by LC-MS, ESI *m/z*: 634.0 $[M+H]^+$.

Methyl 11-(4-((1-(2-((4-(3-bromophenyl)thiazol-2-yl)-amino)-2-oxoethyl)-1*H*-1,2,3-triazol-4-yl)methyl)piperazin-1-yl)undecanoate (8l): Off-white solid, yield: 72%, m.p.: 130-133 ºC. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 12.71 (s, 1H), 8.11 (s, 1H), 8.03 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 5.47 (s, 2H), 3.59 (s, 2H), 3.57 (s, 3H), 2.48-2.29 (m, 8H), 2.28 (t, *J* = 7.6 Hz, 4H), 1,57-1.47 (m, 2H), 1.46-1.36 (m, 2H), 1.33-1.18 (m, 12H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 173.34, 165.09, 157.53, 147.23, 136.30, 130.97, 130.49, 128.26, 125.49, 124.54, 121.89, 109.99, 105.24, 57.59, 52.48, 52.26, 51.81, 51.31, 51.11, 33.23, 28.86, 28.83, 28.77, 28.60, 28.40, 26.77, 25.86, 24.38. Purity: 95% by LC-MS, ESI *m/z*: 662.1 $[M+H]^+$.

Antibacterial assay: The synthesized compounds **8a-l** (50 mg/mL) were tested for their antibacterial activity by using two Gram-positive (*S. aureus* MTCC 96*, B. subtilis* MTCC 736) and two Gram-negative organisms (*E. coli* MTCC 443*, P. aeruginosa* MTCC 424). The standard drug ampicillin at 50 µg/mL was used and the solvent used to dissolve the sample was DMSO. The whole experiment was performed in duplicate and the average of inhibition zone diameters were noted.

Antifungal assay: All the synthesized compounds **8a-l** (50 mg/mL) were also tested for their antifungal activity by using two fungi (*Candida albicans* and *A. niger*). The standard drug clotrimazole (100 µg/mL) was used. The experiments were performed twice and the average of inhibition zone diameters were noted.

Molecular docking studies: Molecular docking studies were carried out using the Autodock Vina of PyRx programme, an open-source software tool [37,38]. The binding affinity of the protein-ligand complex was calculated by Autodock vina using an empirical scoring function [39]. A desirable therapeutic target, glucosamine-6-phosphate synthase is essential for the function of microorganism cell membranes, thus the interactions and binding energies of the synthesized compounds with glucosamine-6-phosphate synthase (PDB ID:

2VF5) were studied [40]. Candida pepsin-1, an intriguing thera-peutic target for the suppression of fungus plays an important role in the surface candida infections [41] therefore, the synthe-sized compounds **8a-l** and standard reference clotrimazole were docked into the active site pocket of candidapepsin-1 (PDB ID: 2VF5) [42].

RESULTS AND DISCUSSION

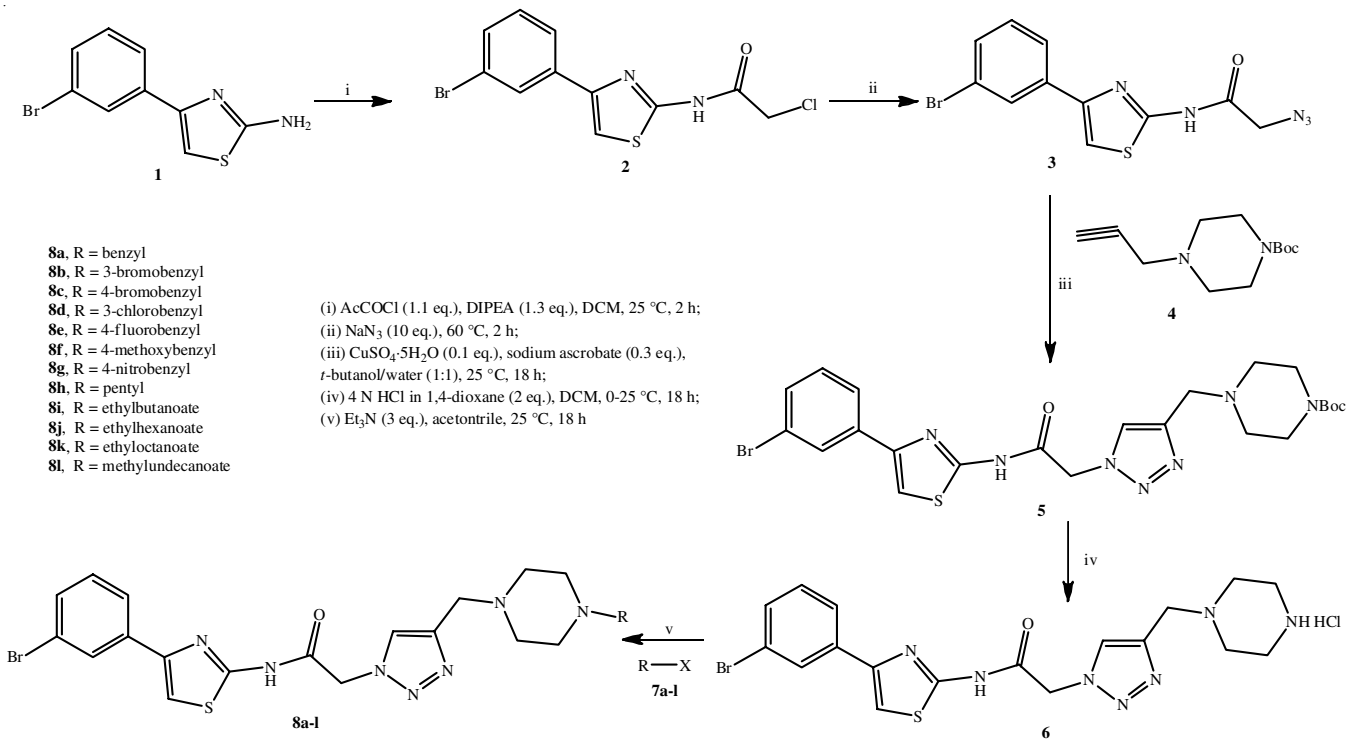
The synthesis of a series of multi-hybrid compounds with thiazole-triazole-piperazine skeleton was carried out by taking 4-(3-bromophenyl)-2-aminothiazole (**1**) as starting compound. The amino group in compound **1** was chloroacylated with chloroacetyl chloride in dichloromethane employing DIPEA as base for 2 h at 25 ºC and gave chloroacetamide derivative **2**, which further gave 2-azido acetamide (**3**) when reacted with NaN_3 in DMF at 60 ºC. Azido compound **3** and *tert.*-butyl-4-(prop-2-yn-1-yl)piperazine-1-carboxylate (**4**) underwent $CuSO_4{\cdot}5H_2O$ catalyzed 1,3-dipolar cycloaddition reaction in the presence of sodium ascorbate in *tert.*-butanol/water (1:1, v/v) to afford new thiazolyl triazolyl N-Boc-piperazine derivative **5**. The click reaction product was confirmed by its spectral data.

^{1}H NMR spectrum of **5** showed a singlet at δ 12.81 ppm corresponding to NH proton of the amide. Further singlets at δ 7.83, 5.48, 3.31 and 1.39 ppm were due to triazolyl, -COC$\underline{H}_2$, N-CH_2- (triazolyl and piperazine connecting methylene protons) and Boc protons, respectively. The $[M-H]^+$ peak is observed at *m/z* 559.8 in ESI LC-MS spectrum of compound **5**.

The key intermediate hydrochloride **6** was prepared from Boc deprotection of **5** with 4 N HCl. Compound **6** was confirmed by its spectral data. ^{1}H NMR spectrum of compound **6** exhibited characteristic singlet signals at δ 8.54, 7.85, 5.61 and 4.58 ppm correspond to thiazole, triazolyl, -COCH_2- and N-CH_2- protons. In its mass spectrum, $[M+H]^+$ and $[M+2H]^+$ peaks are appeared at *m/z* 462.0 and 464.1. The hybrid acetamide **8a** was obtained, when compound **6** reacted with benzyl chloride (**7a**) using Et_3N as a base in acetonitrile at 25 ºC for 18 h. Further, the target multi-hybrid compounds **8b-l** were synthesized using various substituted benzyl halides **7b-f** and aliphatic halides **7g-l** as haloalkane source (**Scheme-I**). The structures for the synthe-sized all targets **8a-l** are confirmed by the spectral data. ^{1}H NMR spectra of compound **8a** showed singlet signals δ 12.75, 8.02, 7.83, 5.46, 3.58, 3.47 ppm corresponds to –CONH-(amide), thiazole, triazole protons, -COC$\underline{H}_2$-, Ph-C$\underline{H}_2$- and N-C$\underline{H}_2$- protons. Multiplet signals were in the range δ 7.34-7.21 and 2.48-2.30 ppm corresponds to the benzylic aromatic and piperazine protons. The carbon signals at δ 165.09, 61.94, 52.42, 52.36, 52.12, 51.31 ppm corresponds to amide carbonyl, Ar-$\underline{C}H_2$, piperazine ring carbons, N-$\underline{C}H_2$- and CO$\underline{C}H_2$- carbons respectively.

Antibacterial activity: All the synthesized compounds **8a-l** were tested for their antimicrobial activity. Among all compounds **8a-l**, benzyl, 3-chlorbenzyl, 4-fluorobenzyl and ethyl hexanoate substituted compounds (**8a**, **8d**, **8e** and **8j**) exhibited good the antibacterial activity against both Gram-positive and Gram-negative organisms, the zone of inhibition of these compounds is a closer value to standard drug ampicillin. The zone of inhibition of synthesized compounds are presented in Table-1. The antibacterial activity of remaining compounds is minimal when compared to that of ampicillin.

Antifungal activity: Most of the compounds had shown good inhibition zones against *Candida albicans* and *A. niger*. Compounds **8d**, **8e**, **8f**, **8h** and **8k** have shown the high antifungal activity and the results are presented in Table-2.



Scheme-I: Synthesis of thiazole-triazole-piperazine analogues

TABLE-1
ZONE OF INHIBITION OF
COMPOUNDS **8a-l** AGAINST BACTERIA

Compound[a]	Inhibition zone diameter (mm)			
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*
8a	14	14	13	14
8b	11	10	11	11
8c	11	12	10	10
8d	15	14	14	15
8e	15	15	15	14
8f	12	11	12	12
8g	13	13	12	12
8h	12	11	12	12
8i	NA	NA	NA	NA
8j	15	14	15	14
8k	12	12	11	12
8l	12	12	11	12
Ampicillin	24	25	24	25

[a]Concentration of the samples is in 50 µg/mL.

TABLE-2
ZONE OF INHIBITION OF COMPOUNDS **8a-l** AGAINST FUNGI

Compound[a]	Inhibition zone diameter (mm)	
	Candida albicans	*A. niger*
8a	15	10
8b	8	8
8c	15	11
8d	18	10
8e	17	11
8f	16	10
8g	15	11
8h	17	12
8i	14	13
8j	16	14
8k	10	9
8l	26	24

[a]Concentration of the samples is in 50 µg/mL.

Molecular docking with glucosamin-6-phosphate synthase (GlmS): Glucosamine-6-phosphate synthase is an attractive drug target as it plays an important role in microbial cell membrane by converting fructose 6-phosphate into glucosamine 6-phosphate in the presence of glutamine [43]. The title compounds **8a-l** were docked into the active site pocket of glucosamine-6-phosphate synthase (PDB ID: 2VF5) [40] along with standard reference ampicillin. The binding energies of compounds are ranging from -7.0 to -8.4 Kcal/mol, the binding interactions of ligands **8a-l** with GlmS are given in Table-3.

The docking scores of all the synthesized compounds are comparable to ampicillin score -7.4 Kcal/mol. Except compound **8a**, all other compounds indicated H-bond as well as hydrophobic interactions in cavity of target GlmS. Compound **8e** scored the highest binding affinity value of -8.4 Kcal/mol, which demonstrated two H-bonds interactions with Asp474, Asn522, a halogen bond interaction with Asp432 and other hydrophobic interactions (Fig. 2). Whereas standard reference ampicillin scored binding affinity of -7.4 Kcal/mol and indicated H-bond interactions with Gln475, Val567 and hydrophobic interactions with Arg472, Asp474, Tyr576 of GlmS (Fig. 3).

Molecular docking with candidapepsin-1: Candidapepsin-1 play a major role in superficial candida infections [41], as a reason it is an interesting drug target for inhibition of fungi [42]. The synthesized compound **8a-l** and standard reference clotrimazole docked into the active site site of candidapepsin-1 (PDB ID: 2VF5) [43], which have exhibited the effective binding scores (Table-4).

Compound **8e** scored the highest binding affinity value of -9.7 Kcal/mol, it demonstrated H-bond interactions with Gly220, Thr221 and hydrophobic interactions with Ile30, Asp32, Tyr84, Asp86, Ile119, Asp218, Thr222, Ala335 of candidapepsin (Fig. 4). The standard drug clotrimazole scored binding affinity of -6.7 Kcal/mol, it showed only hydrophobic interactions with Phe251, Leu283, Ser284, Ala286, Tyr291 of candidapepsin-1 (Fig. 5).

Pharmacokinetics evaluation: Oral bioavailability is an important aspect in development of new drug candidates. Absorption, distribution, metabolism and excretion properties were evaluated by SwissADME web server protocol [44]. The octanol/water partition coefficient (Log $P_{w/o}$) values were predi-

TABLE-3
INTERACTIONS OF SYNTHESIZED MOLECULES WITH GLUCOSAMINE-6-PHOSPHATE
SYNTHASE (PDB ID: 2VF5) AND THEIR BINDING ENERGIES

Compound	Binding energy (Kcal/mol)	Interacting amino acids	
		H-bond	Hydrophobic
8a	-7.9	–	Tyr312, Ser316, Asp474, Ala520, Ala551, Phe553, Glu569
8b	-8.2	Asp474	Tyr312, Ser316, Asp474, Ala520, Asn522, Ala551, Phe553
8c	-8.0	Asp474	Tyr312, Arg472, Gly473, Asp474, Ala520, Pro521, Ala551
8d	-8.2	Asp474, Asn522	Tyr312, Ser316, Asp474, Ala520, Ala551
8e	-8.4	Gly436, Asp474	Leu317, Asp432, Asp474, Ala520, His566, Glu569, Val570, Ala572
8f	-7.8	Asp474	Tyr312, Arg472, Asp474, Ala520, Pro521, Ala551
8g	-8.0	Ser316, Gly436	Leu317, Asp432, Asp474, Ala520, His566, Glu569, Val570, Ala572
8h	-7.4	Asp474, Asn522	Trp313, Ser316, Arg472, Asp474, Ala520, Ala551, Phe553, Val570, Ala572
8i	-7.2	Asp548, Glu569	Asp474, Ala520, Glu569, Val570, Tyr576
8j	-8.3	Asp474	Tyr312, Trp313, Leu317, Arg472, Asp474, Gln575, Ala520, Asp548, Ala551, His566, Val570, Ala572,
8k	-7.0	Asp474, Asn523	Trp313, Leu317, Arg472, Gly473, Asp474, Ala520, Asn522, Ala551, Glu569, Ala572, Tyr576
8l	-7.7	Ser316, Asp474, Glu569	Leu317, His435, Asp474, Ala520, His566, Glu569, Val570, Ala572
Ampicillin	-7.4	Gln475, Val567	Arg472, Asp474, Tyr576

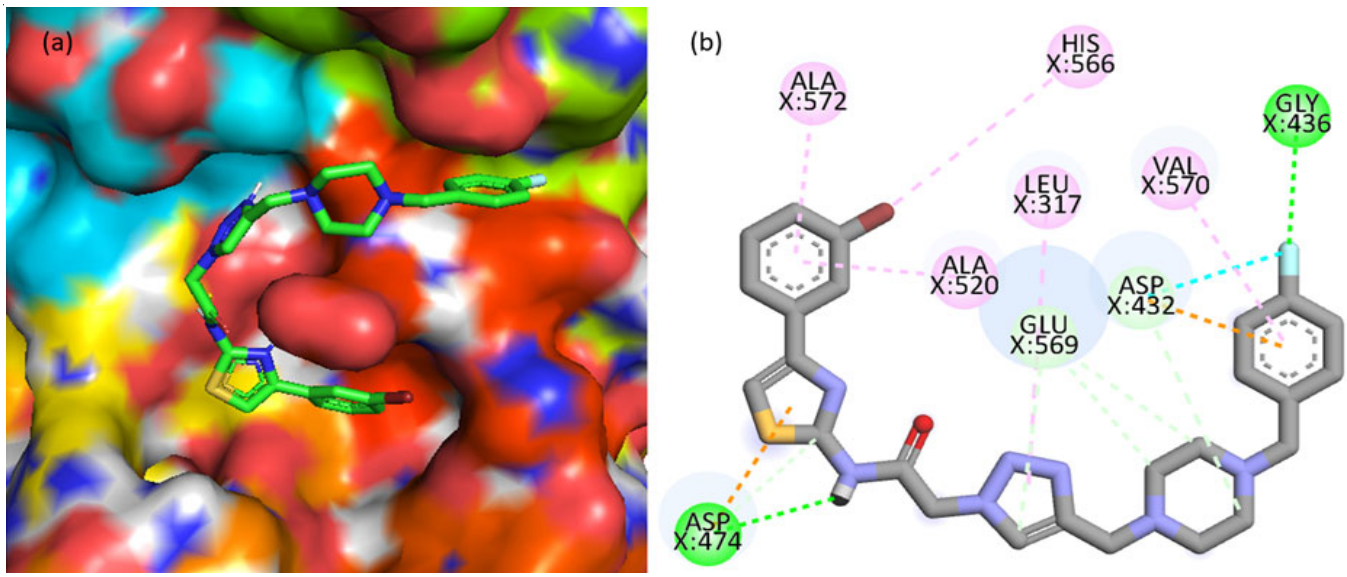


Fig. 2. (a) Docking pose and (b) 2D interactions of compound **8e** in a cavity of glucosamine-6-phosphate (PDB ID: 2VF5)

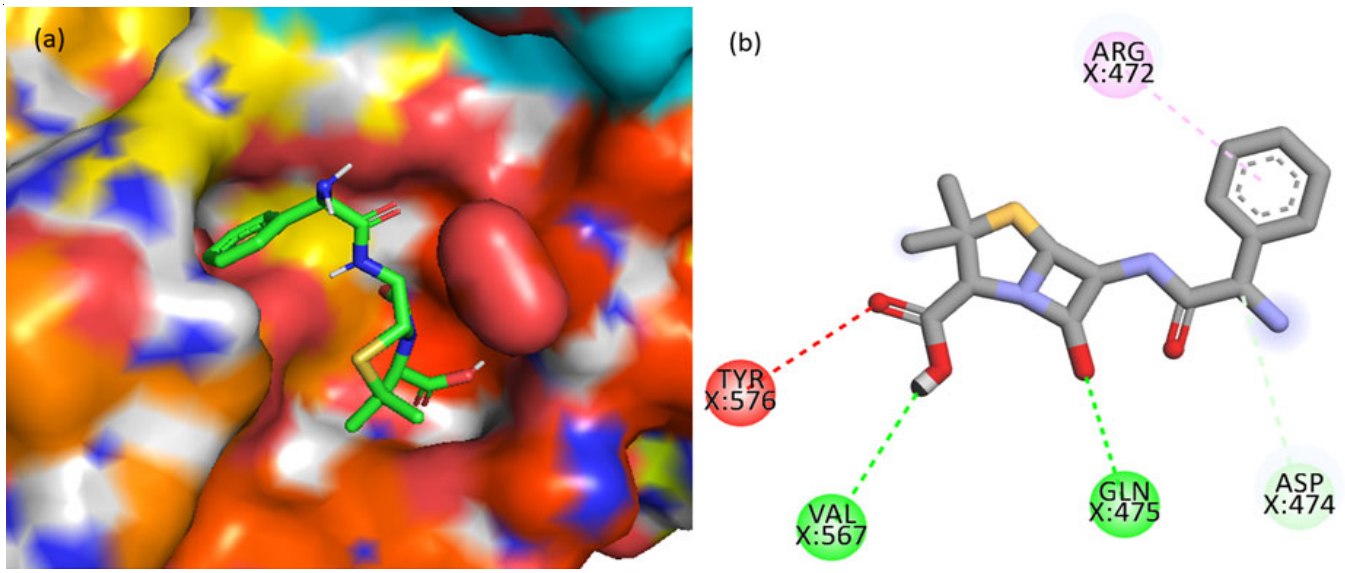


Fig. 3. (a) Docking pose and (b) 2D interactions of ampicillin in cavity of glucosamine-6-phosphate (PDB ID: 2VF5)

TABLE-4
DOCKING SCORE AND BINDING INTERACTIONS OF NEWLY SYNTHESIZED COMPOUNDS AGAINST CANDIAPESPIN-1 (PDB ID: 2QZW)

Compound	Binding energy (Kcal/mol)	Interacting amino acids	
		H-bond	Hydrophobic
8a	-9.1	Asp32, Gly220	Val12, Ile30, Asp86, Pro120, Ile123, Thr221, Tyr225
8b	-9.2	Gly85, Asp86, Gly220	Lys49, Arg51, Gln54, Phe58, Asp86, Ile123, Thr221, Tyr225
8c	-9	Asp86, Ser88	Lys49, Tyr84, Asp86, Ser118, Ile119, Asp218, Gly220, Ala335
8d	-9	Asp86, Thr221	Ser13, Gly85, Asp86, Ile119, Pro120, Asp218, Ala335
8e	-9.7	Gly220, Thr221	Ile30, Asp32, Tyr84, Asp86, Ile119, Asp218, Thr222, Ala335
8f	-9.2	Gly220, Thr221	Ile30, Asp32, Gly85, Asp86, Glu193, Asp218, Gly220, Tyr225, Ser301, Ser336
8g	-9.4	Thr221, Thr222	Ile30, Asp86, Ile119, Asp218, Gly220, Tyr225, Ala335
8h	-8.1	Asp86, Ser88	Tyr84, Asp86, Ser118, Ile119, Ile123, Asp218, Gly220, Ala335
8i	-8.2	Asp32, Gly220	Val12, Tyr84, Asp86, Ser88, Pro120, Asp218, Thr221, Ser301
8j	-7.8	Lys49, Asp86, Ser88	Arg51, Tyr84, Asp86, Ser88, Ile119, Asp218, Ala335
8k	-7.1	Asp86, Ser88, Thr222	Tyr84, Asp86, Ser118, Ile119, Ile123, Asp218, Gly220, Thr221, Ala335
8l	-7.6	Gly85, Thr221, Thr222, Ser301, Ser334	Pro4, Ile30, Tyr84, Gly85, Asp86, Ile123, Gly220, Thr221, Thr222, Tyr225, Ala303, Ser334
Clotrimazole	-6.7	–	Phe251, Leu283, Ser284, Ala286, Tyr291

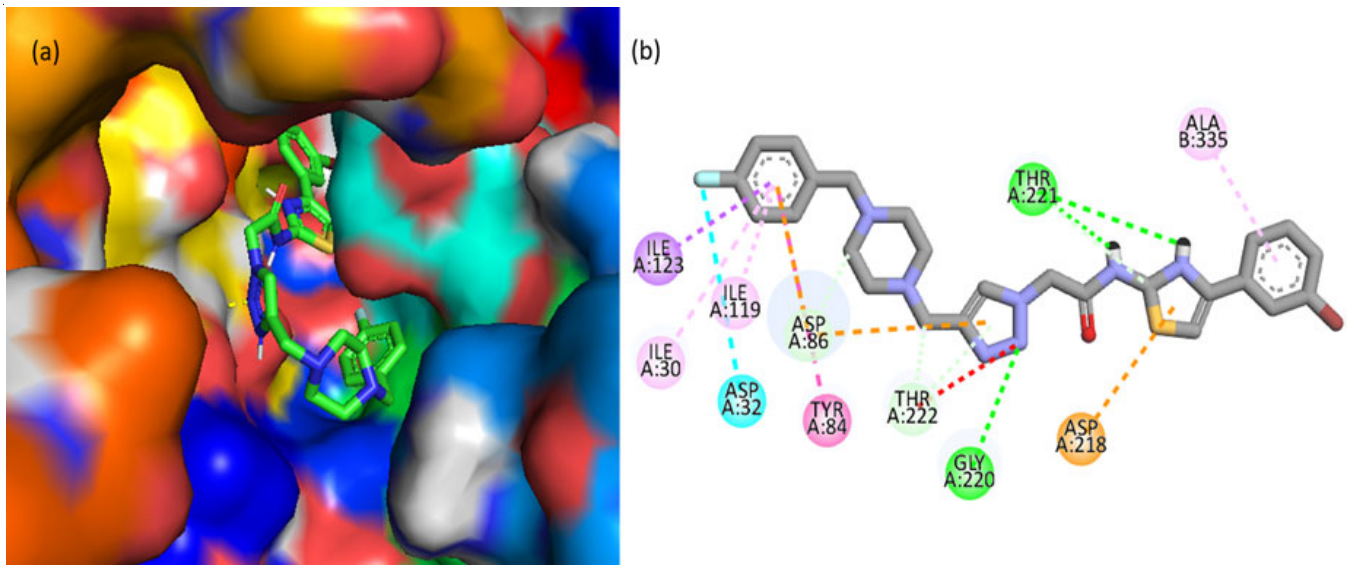


Fig. 4. (a) Docking pose and (b) 2D interactions of compound **8e** in cavity of candidapespin-1 (PDB ID: 2QZW)

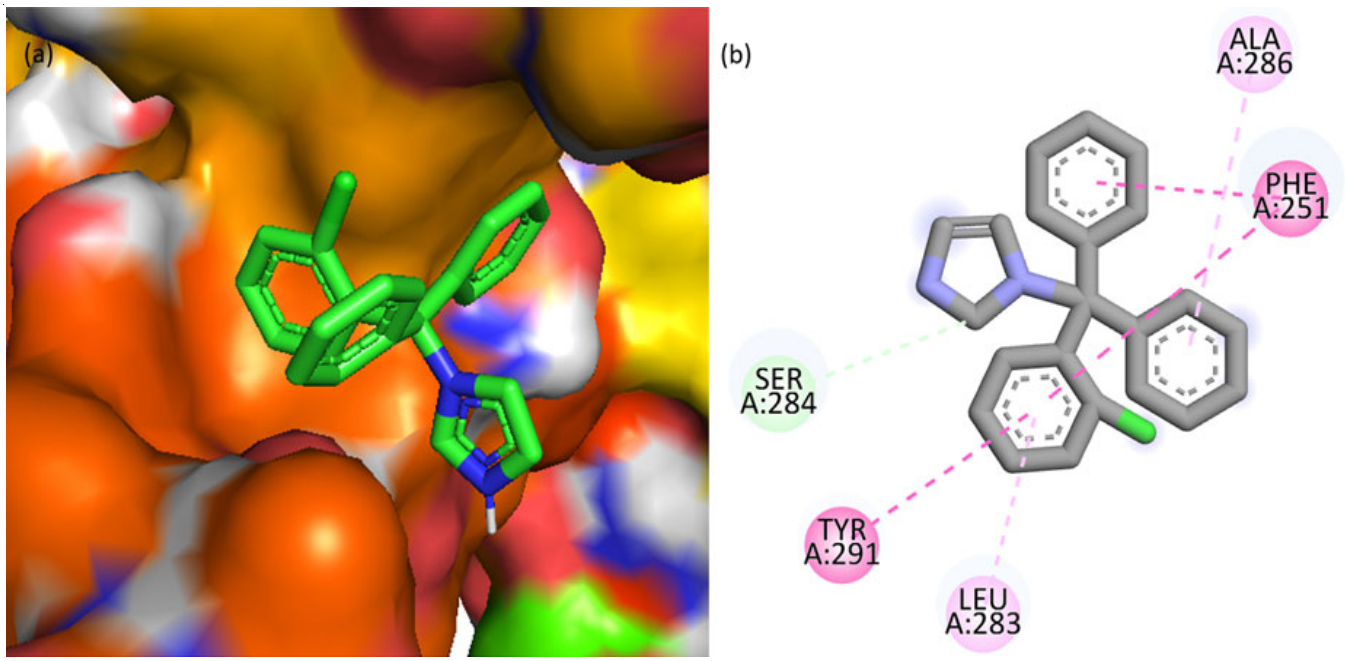


Fig. 5. (a) Docking pose and (b) 2D interactions of clotrimazole in cavity of candidapespin-1 (PDB ID: 2QZW)

cted in the range of 2.68-4.85 and as per the essential condition of Lipinski's rule of five. The molecular weight of compounds **8a-l** was > 500 g/mol, although these molecules have exhibited good inhibition activity experimentally (Table-5). The predicted rotatable bonds were in the range of 9-19, H-bond acceptors were ≤ 10 and only one H-bond donor is present. The topological polar surface (TSPA) of analogous were in the range of 107.42-153.24; these lower TSPA values indicate the acceptable range of results. The violations of Lipinski's rule were zero. The synthetic availability score of all analogues was found to be < 10, it confirms that they can be synthesized easily [45]. The pharmacokinetic evaluation of **8a-l** revealed that all molecules have favourable drug-likeness properties and could be considered as therapeutic agents.

Conclusion

Multi-hybrid compounds **8a-l** containing thiazole-triazole-piperazine as three privileged scaffolds were synthesized starting from copper catalyzed 1,3-dipolar cycloaddition reaction of thiazole-based azide **3** and Boc-protected piperazine based alkyne **4** in the presence of sodium ascorbate. Removal of Boc group followed by the alkylation of piperazine in hybrid derivatives gave the titled multi-heterocycles. All the synthesized compounds were confirmed using spectral techniques and also screened for their antimicrobial activity. Most of the compounds showed promising antimicrobial activity in antimicrobial test. All the molecules showed good to moderate activity and supported by performing the pharmacokinetics evaluation and molecular docking studies.

TABLE-5
PHARMACOKINETICS EVALUATION RESULTS OF COMPOUNDS **8a-l**

Compound	m.w. (range ≤ 500)	Rotatable bonds (range 1-10)	H-bond acceptors (range ≤ 10)	H-bond donors (range ≤ 5)	TPSA	Log $P_{o/w}$ (range ≤ 5)	Molar refractivity (range 40-130)	QPLogS (solubility)	Lipinski	Bioavailability score (range 0.4-0.6)	Synthetic accessibility
8a	552.49	9	6	1	107.42	3.26	148.92	-5.40	Yes	0.55	4.00
8b	631.39	9	6	1	107.42	3.98	156.62	-6.31	Yes	0.55	4.01
8c	631.39	9	6	1	107.42	3.99	156.62	-6.31	Yes	0.55	4.00
8d	586.93	9	6	1	107.42	3.84	153.93	-6.00	Yes	0.55	4.00
8e	570.48	9	7	1	107.42	3.51	148.88	-5.56	Yes	0.55	3.99
8f	582.52	10	7	1	116.65	3.26	155.41	-5.47	Yes	0.55	4.11
8g	597.49	10	8	1	153.24	2.68	157.74	-5.47	Yes	0.17	4.08
8h	532.50	11	6	1	107.42	3.42	143.66	-5.22	Yes	0.55	4.05
8i	576.51	13	8	1	133.72	2.89	149.75	-4.55	Yes	0.55	4.20
8j	604.56	15	8	1	133.72	3.51	159.37	-5.03	Yes	0.55	4.41
8k	660.67	19	8	1	133.72	4.85	178.60	-6.56	Yes	0.55	4.89
8l	660.67	19	8	1	133.72	4.85	178.60	-6.56	Yes	0.55	4.89

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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